CHLOROQUINE PSYCHOSIS: A CHEMICAL PSYCHOSIS?

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Psychotic states are mimicked by the use of many drugs including amphetamines, cannabis, lysergic acid diethylamide, psilocybin, mescaline, isoniazid, and L-dopa. A paranoid psychotic picture in a clear sensorium is characteristic of amphetamine psychosis. In developing countries, malaria among other diseases is a frequent indicator of chloroquine administration. The present communication reports a series of chloroquine-induced psychosis in a clear sensorium simulating affective illness, such as mania, mixed affective states, or depression. The psychosis disappeared after cessation of the drug, combined with or without the use of low dosage phenothiazines in excited patients. From our cases, two types of presentation of chloroquine psychosis could be seen: (1) psychic with clear sensorium, mood changes, alteration in motor activity, delusions, and hallucinations; and (2) psycho-organic with clouded sensorium, disorientation, and fleeting hallucinations. The precise nature of the mechanism of the psychosis is not clear because of the limited number of reported cases.

Chloroquine, as a therapeutic agent, is being used for malaria, extra-intestinal amoebiasis, giardiasis, rheumatoid arthritis, discoid lupus, photoallergic reactions, and cardiac arrhythmias. Its use is associated with various side effects. Between 1978 and 1980 the authors found at least ten cases of psychiatric complications associated with chloroquine therapy. This has been mentioned by several others.[1-10]

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The various psychiatric manifestations associated with chloroquine use have been described as personality changes,[1] depression, depersonalization, neurotic symptoms,[11,12] and florid psychosis.[2-10] Suicide also has been included as a possible psychiatric complication of chloroquine use.[13,14] Antimalarials also might produce a syndrome like amok.[15] The present article describes the various psychiatric manifestations presented by ten of our patients, the largest series of cases so presented.

PHARMACOLOGY

In 1934, chloroquine was synthesized in Germany as Resochin. The 7-chloro-4-[[diethylamino-1-methylbutyl]amino] quinoline was designated as SR 7618 for the first time in 1944 by workers in the United States and was later named chloroquine. The chloride atom in the seventh position of the quinoline nucleus appears to be crucial to the antimalarial activity. The D-isomer is less toxic than the L-isomer in mammals. Its significant effect is due to its interaction with double stranded DNA. It inhibits DNA polymerase markedly and RNA polymerase less so, by combining with the DNA primer.[16] There is a progressive degradation of RNA by chloroquine in the subcellular particles, notably the ribosomes. The ring system of chloroquine fits nicely upon a quanine-cytosine base pair of DNA.

After a single oral dose, maximum plasma concentration is reached in one to two hours. Its half life is five days. Seventy percent of chloroquine is excreted as unchanged chloroquine. Small amounts can be found in urine for as long as five years.[16-18] The rest is metabolized as desethyl chloroquine, bis deethyl chloroquine, a carboxylic acid derivative, and other metabolic products. In animals, high concentration occurs in the liver, spleen, kidneys, and lungs (200 to 700 times the plasma concentration); in the brain; and in the spinal cord (10 to 30

times plasma concentration).[16,18-22] Various side effects associated with its use are reported in the literature.[16,18,20,21,23,24] The psychiatric manifestations are listed in Table 1. Reviews on the behavioral toxicity of chloroquine are very few,[13-17] though it has been observed that the margin between therapeutic and toxic doses of chloroquine is rather narrow.[16,25-27]

DATA PRESENTATION

The patients seen in this series manifested a wide range of psychiatric symptoms (Table 2), which are either psychotic in nature, such as insomnia, irritability, impulsivity, verbal and physical aggressiveness, psychomotor hyperactivity, depressed affect, hallucinations, and suicidal and paranoid ideas; or psycho-organic, such as confusion and clouded sensorium. The frequency with which these symptoms were observed is summarized in Table 3. Similar symptoms also were observed in earlier reports.[1-11,13,16,17,20,21,24,28]

In the present series, the symptoms were not dose related, though earlier reports suggested that they usually varied between a total dose of 2 to 6 gm of chloroquine sulphate or phosphate. The latent period has been calculated to be from 2 hours to 40 days at the above dosage. In all of our patients, symptoms appeared between the third and tenth day of chloroquine administration. Symptoms usually disappeared within a week following discontinuation of the drug. Psychiatric manifestations in our patients lasted for one to two weeks, and all patients made a quick recovery with much smaller doses of chlorpromazine (25 mg to 300 mg) in addition to cessation of the drug.

Age and sex did not appear to be predisposing factors (perhaps the numbers were too small). None of these patients had a previous individual or family history of mental illness.

DISCUSSION

The precise mechanism for psychiatric manifestations is unknown. The premorbid personality or idiosyncratic response has been suggested to be a possible explanation.[7,9,10] It also has been suggested that the psychosis may be related to the possible acetylcholinesterase inhibitory action of chloroquine.[3] The psychotic picture in a clear sensorium seen after chloroquine use resembles many features of affective disorders, primarily mania, though a few cases present with organic brain syndrome symptomatology. It can be speculated that chloroquine might influence the dopaminergic system in the brain with alteration in dopamine levels, a hyperdopaminergic response in most cases. Norepinephrine and serotonin might play a role, as in the case of affective disorders. If it involves the dopaminergic system, can there be some role for endogenous peptides in producing the symptomatology after chloroquine use? It is well established that amphetamine can produce a paranoid psychosis in a clear sensorium which is indistinguishable from paranoid schizophrenia, and the drug can be employed for producing model psychosis. Chloroquine use can produce an affective illness type picture in a clear sensorium in most cases. It is also speculated that it can be used as a model for inducing psychosis with affective symptomatology. Further studies must be done in this area to prove or disprove this speculation.

TABLE 1. PSYCHIATRIC MANIFESTIONS OF CHLOROQUINE

Psycho-organic Symptoms	Clouding of sensorium, disorientation, confabulation, fleeting hallucinations
Psychotic Symptoms	Restlessness, agitation, outbursts of violence, depression, suicidal ideas, suicide, delusions of persecution and grandeur, hallucinations (visual and auditory), elation, irritability, perplexity or rapid fluctuation of mood, amok syndrome, irrelevant talk, insomnia, personality change

The issue is of especial concern because, in 1976, out of 888 million people living in the originally malaria prone areas, 573 million (1.65 percent) were under surveillance. In South East Asia 6,539,000 cases of malaria were detected at the end of 1976,[29] for which chloroquine was one of the main drugs used for treatment. Hence, the possibilities of chemical psychoses, which perhaps went unrecognized or unreported, seem to be a real danger to which greater attention must be paid.

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TABLE 2. DISTRIBUTION OF SYMPTOMS AND SIGNS (10 CASES)

Symptoms and Signs	Number of Cases	Percentage
Psychomotor hyperactivity	5	50
Elation	3	30
Depression	2	20
Variable mood	3	30
Insomnia	10	100
Paranoid ideas (delusions)	9	90
Grandiose ideas	5	50
Hallucinations	5	50
Suicidal ideas	2	20
Irrelevant talk	7	70
Disorientation/clouding of sensorium	3	30

TABLE 3. PSYCHIATRIC MANIFESTATIONS OF CHLOROQUINE USE

Patient	Age	Sex	Total Dose of Chloroquine (base)	Onset (days)	Mental State
M.R.	19	F	2 gm	10	Excessive irrelevant talking, psychomotor hyperactivity, paranoid ideas, unprovoked laughing and crying, rapid fluctuation of mood from elation to depression, outbursts of anger, insomnia
P.A.	20	M	1.8 gm	4	Rapid variability of mood from elation to depression, disoriented, visual and auditory hallucinations, paranoid ideas, insomnia
B.	18	F	1.5 gm	3	Excessive irrelevant talking, psychomotor hyperactivity, elation, grandiosity, insomnia
B.S.	25	M	1.5 gm	4	Psychomotor hyperactivity, aggressiveness, paranoid delusion, irrelevant talk, fleeting auditory and visual hallucinations, insomnia
S.P.	32	F	1.8 gm	5	Depressed, suicidal ideas, paranoid delusions, occasional grandiose ideas, visual and auditory hallucinations (fleeting), disorientation, irrelevant talk, insomnia
G.K.	20	M	1.5 gm	4	Excessive irrelevant talking, ideas of reference, paranoid ideas, easy irritability, auditory hallucinations, grandiose ideas, insomnia
S.B.	25	M	1.8 gm	6	Disoriented, paranoid delusions, visual and auditory hallucinations, rapid fluctuation of mood, insomnia
M.S.	28	M	1.5 gm	4	Psychomotor hyperactivity, grandiosity, excessive and irrelevant talk, paranoid ideas, elation with periods of irritability
L.D.	40	F	1.5 gm	4	Depressed, suicidal ideas, weeping spells, paranoid ideas, insomnia
T.I.	24	M	1.5 gm	4	Psychomotor hyperactivity, elation with periods of easy irritability, grandiose and paranoid ideas, excessive and irrelevant talk, insomnia

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